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Slow wave sleep in the chronically fatigued: Power spectra distribution patterns in chronic fatigue syndrome and primary insomnia

Daniel Neu [a,b,*,1], Olivier Mairesse [a,b,c,d,*,1], Paul Verbanck [a,b], Olivier Le Bon [b,e]

[a] Brugmann University Hospital, Sleep Laboratory & Unit for Chronobiology U78, Université Libre de Bruxelles (U.L.B.), Brussels, Belgium
[b] UNI, ULB Neurosciences Institute, Faculty of Medicine, Laboratory for Medical Psychology ULB312, Université Libre de Bruxelles (U.L.B.), Brussels, Belgium
[c] Department of Experimental and Applied Psychology (EXTO), Vrije Universiteit Brussel (V.U.B.), Brussels, Belgium
[d] Royal Military Academy, Department LIFE, Brussels, Belgium
[e] Tivoli University Hospital, Department of Psychiatry, U.L.B., La Louvière, Belgium

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HIGHLIGHTS

- Evidence for similarly lower central ultra slow (US) delta power (0.3–0.79 Hz) proportions during slow wave sleep (SWS) in both primary insomnia and chronic fatigue syndrome in comparison to controls.
- Lower US power proportions relate mainly to perceived sleep quality impairment and daytime fatigue intensity.
- Clinical distinction between both conditions relates to a different frontal EEG power distribution during SWS in primary insomnia.

ABSTRACT

Objectives: To investigate slow wave sleep (SWS) spectral power proportions in distinct clinical conditions sharing non-restorative sleep and fatigue complaints without excessive daytime sleepiness (EDS), namely the chronic fatigue syndrome (CFS) and primary insomnia (PI). Impaired sleep homeostasis has been suspected in both CFS and PI.
Methods: We compared perceived sleep quality, fatigue and sleepiness symptom-intensities, polysomnography (PSG) and SWS spectral power distributions of drug-free CFS and PI patients without comorbid sleep or mental disorders, with a good sleeper control group.
Results: Higher fatigue without EDS and impaired perceived sleep quality were confirmed in both patient groups. PSG mainly differed in sleep fragmentation and SWS durations. Spectral analysis revealed a similar decrease in central ultra slow power (0.3–0.79 Hz) proportion during SWS for both CFS and PI and an increase in frontal power proportions of faster frequencies during SWS in PI only. The latter was correlated to affective symptoms whereas lower central ultra slow power proportions were related to fatigue severity and sleep quality impairment.
Conclusions: In combination with normal (PI) or even increased SWS durations (CFS), we found consistent evidence for lower proportions of slow oscillations during SWS in PI and CFS.
Significance: Observing normal or increased SWS durations but lower proportions of ultra slow power, our findings suggest a possible quantitative compensation of altered homeostatic regulation.

1. Introduction

Sleepiness and excessive daytime sleepiness (EDS) in particular have been related to non-restorative sleep (NRS) complaints and to impaired sleep homeostasis in primary sleep disorders (PSD) (Stone et al., 2008). However, even in the absence of EDS and of

* Corresponding authors at: Brugmann University Hospital, Sleep Laboratory & Unit for Chronobiology U78, Université Libre de Bruxelles, 4, Arthur Van Gehuchten Square – Building Hh, 1020 Brussels, Belgium. Tel.: +32 24772554; fax: +32 24772162.
E-mail addresses: daniel.neu@chu-brugmann.be (D. Neu), olivier.mairesse@chu-brugmann.be (O. Mairesse).
[1] Both authors contributed equally to this work.

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a comorbid PSD, chronic fatigue syndrome (CFS) and primary insomnia (PI) patients also systematically complain of NRS (Wilkinson and Shapiro, 2012). In addition, given that chronic daytime fatigue and EDS are different phenomena both related to NRS complaints, it seems in turn unlikely for their respective relations to sleep being of the same nature (Neu et al., 2014).

Chronic fatigue is known to be different from EDS. In contrast to sleepiness or EDS, its relationships to sleep remain disputed. Chronic fatigue has been described as being associated to systemic disorders and being independent from primary sleep disorders (Hossain et al., 2005; Neu et al., 2010a). The chronic fatigue syndrome (CFS) is a nosographically described exclusionary syndrome without known etiology. Its main symptoms feature chronic fatigue, without EDS and not alleviated by rest, effort intolerance or post-exertion malaise and complaints of non-restorative sleep (NRS) or un-refreshing morning arousals. NRS is systematically reported in CFS despite adequate and stable timing of sleep periods and even despite the absence of sleep maintenance difficulties or other identifiable PSD based on polysomnographic (PSG) recordings. The latter is sometimes referred to 'pure' CFS patients (i.e. without PSD and without EDS) (Neu et al., 2007, 2008; Mariman et al., 2013). Additional symptoms comprise flu-like symptoms, diffuse muscle or joint pain and cognitive complaints. Previous study results about sleep in CFS reported similar (Majer et al., 2007) or increased SWS (Kishi et al., 2011; Neu et al., 2009), higher NREM alpha power (Moldofsky et al., 1975), lower delta power (Decker et al., 2009) or increased relative delta power during SWS (Guilleminault et al., 2006) and idiopathic micro-arousals (Neu et al., 2008; Le Bon et al., 2012). Most discrepancies among these studies can be attributed to methodological issues, mainly concerning exclusion criteria for comorbid PSDs or to different approaches in assessing spectral power (Mariman et al., 2013; Le Bon et al., 2012). At last, a possible dysfunction of sleep homeostasis in CFS has previously been suggested in a report about CFS-discordant twins. The latter showed a failure of adequate homeostatic response after sleep deprivation in the CFS-diagnosed twins only (Armitage et al., 2007). Moreover, a central decrease of slow oscillation (<1 Hz) spectral power (referred to as ultra slow delta or US) in comparison to healthy controls (Le Bon et al., 2012) and to a PSD (Neu et al., 2014) extended the hypothesis about a potential homeostatic dysfunction in two independent samples of CFS without EDS and without PSD. However, it remains unclear whether lower US power during SWS is a common phenomenon associated to chronic fatigue in general or is solely related to etiopathogenesis of CFS.

PI is also essentially a syndrome, based on complaints of sleep initiation or maintenance difficulties, possible early morning awakenings and complaints of NRS (Moul et al., 2002) and daytime fatigue (Yang et al., 2009; Valko et al., 2008). Conceptual description of PI has mainly focused on hyperarousal following a neurocognitive model comprising physiological arousal and cognitive arousal. Consecutively, previous PSG studies mainly reported increased power in higher sleep-EEG frequency bands (i.e. sigma, beta) in PI (Feige et al., 2013; Spiegelhalder et al., 2012; Cervena et al., 2013). Nevertheless, there is currently also sufficient evidence suggesting dysfunction of sleep homeostasis in PI (Pigeon and Perlis, 2006). Pigeon and Perlis (2006) described several lines of evidence for homeostatic dysfunction in a recent review about PI: lower increase or rebound of SWS than controls after sleep deprivation, reduced SWS pressure, reduced delta power without reduced SWS duration, longer SWS-latencies, normal or even decreased objective daytime sleepiness as measured by multiple sleep latency tests (MSLTs), less sleepiness than controls after sleep deprivation and differences of sleep stage proportion increases during recovery after total sleep deprivation. Hence, PI is therefore also a valid model of daytime fatigue which is not EDS (lower sleep pressure, difficulties of sleep initiation despite complaints of insufficient sleep or NRS). Disregarding a prior report mentioning decreased low-frequency and increased higher frequency NREM EEG in subjective insomnia (Krystal et al., 2002), a specific reduction of NREM sleep slow oscillations has however currently only been described in a case report of fatal familial insomnia (Gemignani et al., 2012).

In contrast to currently prevailing assumptions of chronic daytime fatigue being rather independent from sleep or presenting at least with more indirect relations to sleep than daytime sleepiness, it might therefore well be that chronic fatigue which is not sleepiness presents with associated impaired sleep homeostasis, at least in certain clinical conditions.

Thus, based upon these insights about sleep complaints' related chronic daytime fatigue without sleepiness in CFS and in PI and potential homeostatic dysfunction, we hypothesize that different chronic daytime fatigue associated conditions present with potentially similar dysfunction in sleep homeostasis with respect to slow wave activity (SWA). As such, lower US power during SWS might be associated to chronic fatigue in different conditions irrespective of syndromic definition, nosography or even etiology. In contrast to sleep-resolving sleepiness, the latter might therefore indicate a possible common underlying pathophysiology of sleep related maintenance of chronic daytime fatigue that does not resolve with sleep.

2. Methods

2.1. Setting

The present study was carried out in a population assigned to a general university hospital's sleep laboratory. Inclusion of subjects was based on clinical and technical selection criteria (see below) and the results of a full night polysomnographic recording (PSG).

2.2. Participants

CFS patients and control subjects were in large parts similar to a previous study sample described in detail elsewhere (Neu et al., 2014). Based on PSG recordings, medical files and demographical data, PI patients were carefully selected on a retrospective basis, in order to correspond as close as possible with the two other groups. CFS patients were recruited according to CDC diagnostic criteria (Fukuda et al., 1994) without co-morbid mental disorders or PI according to DSM IV criteria (APA, 2000) and after exclusion of a primary sleep disorder (PSD). Further inclusion criteria for all subjects were a minimum time in bed (TIB) of 300 min and a minimum total sleep time (TST) of 240 min during a full night PSG. All included subjects were free from hypnotics or other relevant neuropsychopharmacological treatment (including antidepressants) for at least 3 weeks prior to recording. Further exclusion criteria were significant co-morbid or overlapping medical conditions (including major depression, bipolar or psychotic disorders) potentially interfering with the above-mentioned daytime conditions and inclusion diagnoses, and treatment essays under PSG recording or any co-morbid sleep disorders. All patients in our lab completed questionnaires about life style and drinking habits. Patients with a consumption of more than two units of alcohol per day were excluded.

Both patient groups were compared to a good sleeper control (GSC) group without NRS, from locally recruited healthy volunteers. They were paid between 100 and 150 Euros by private funding for their participation. Regular sleep-wake schedules were required and shift work was not allowed. No significant somatic condition and no current or past mental disorder were allowed

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in the control group. Further exclusion criteria were identical to those of the patient group.

All participants admitted to the sleep unit were prepared for PSG recording between 9 pm and 11 pm and allowed to retire when they wished. Morning arousal was spontaneous in most cases. All participants got standard physical examination, semi-structured DSM IV (APA, 2000) based clinical interview and underwent psychometric assessment of fatigue, sleepiness and affective symptoms.

According to inclusion and exclusion criteria, 67 subjects were retained for further analysis comprising 30 CFS patients (4 males) and 15 PI patients (5 males), which were compared to 22 GSC (6 males).

The study was approved by the local ethical committee and conducted in accordance with the rules and regulations for the conduct of clinical trials stated by the World Medical Assembly in Helsinki.

2.3. Material

The recordings included electroencephalograms recorded from Fp2-A1, C4-A1, O2-A1, sites, two electrooculograms, submental and bilateral anterior tibial electromyograms. Oral and nasal airflow were recorded by a oro-nasal cannula (Pro-Flow Plus™ Pro-Tech® Mukilteo, WA, USA), respiratory effort was measured by thoracic and abdominal belts (Pro-Tech® CT2™, Mukilteo, WA, USA). Capillary oxygen saturation was monitored by photosensitive finger-oximetry (Nonin® Flexi-Form® II 7000A Nonin Medical Inc, Minneapolis, MN USA and LINOP® Adt Masimo corp. Irvine, CA, USA). All PSG recordings were analyzed on 21'' screens displaying 30 second polysomnograph epochs (Philips Respironics Inc™ Alice5®, Philips Healthcare™, Eindhoven, The Netherlands, European Union) by trained technicians unaware of the aims of the study.

2.4. Polysomnography

Sleep onset latency (SOL) was defined as the time from lights-off to the first 30 s epoch of sleep. Sleep period time (SPT) is the time interval from sleep onset to final awakening. Total sleep time (TST) is defined as SPT minus the total duration of cumulated intra-sleep awakenings (wake time after sleep onset, WASO). Time in bed (TIB) equals the total recording time comprising SPT and SOL (TIB = SPT + SOL where SPT = TST + WASO). The internal sleep efficiency index (SEI), expressed in percent, is defined here as the ratio between TST and SPT (SEI = (TST/SPT) * 100). NREM (Non Rapid Eye Movement) sleep included sleep stages N1, N2 and N3 (or slow wave sleep, SWS). REM (Rapid Eye Movement) sleep latency (REM-LAT) was defined as the time between sleep onset and the first epoch of REM sleep. An episode of sleep apnea was defined as a more than an 80% reduction in airflow for at least 10 s during sleep. A sleep hypopnea was defined as a $\geqslant$30% reduction of airflow amplitude accompanied by either a 3% or greater reduction in oxygen saturation or an arousal. Microarousals (MAOS) were defined according to the American Academy of Sleep Medicine (AASM) criteria (Iber et al., 2007). The microarousal index (MAI) and the periodic limb movement index (PLMI) represented the number of microarousals and periodic leg movements per hour of sleep respectively.

2.5. Sleep EEG power spectra analysis (PSA)

The spectrogram was computed for EEG channels derived data from frontal (Fp2), central (C4) and occipital (O2) electrodes. Effective recording sampling rate for EEG channels was set at 2000 Hz (Alice5®, Philips Respironics Inc™). Each channel was created by computing the spectrum every 6 s and each 6-s spectrum was the average of two spectra, computed on two overlapping windows of 5.12 s (0–5.11 and 0.88–5.99). The signal was multiplied with a 512 point Bartlett window after suppressing the mean from each point in order to remove the 0 Hz component. The Fast Fourier Transform (FFT) was then applied to estimate spectral power and was averaged for the two overlapping segments ($dB^*\mu V^2/Hz$). Six frequency bands were analyzed: Ultra Slow (US) (0.3–0.79 Hz), Delta (0.8–3.9 Hz), Theta (4–7.4 Hz), Alpha (7.5–12.4 Hz), Sigma (12.5–17.9 Hz) and Beta (18–25 Hz). FFT for spectral power was only assessed for epochs visually scored as SWS. Sleep EEG artifacts due to eyes' and muscles' movements were first automatically detected and underwent then a visual analysis of all recorded PSG epochs for scoring accuracy and additional artifact detection in all included subjects prior to FFT and therewith PSA.

2.6. Psychometrics

Self-reporting questionnaires with classical semantic instructions for fatigue and sleepiness were given to all participants on the first day of their stay in our unit at the same daytime (between 5 pm and 7 pm) before polysomnographic recording.

The *Fatigue Severity Scale* (FSS) is a self-reporting tool used to assess symptomatic intensity levels of fatigue and its effect on daily functioning (Krupp et al., 1989). It has been used in many studies investigating fatigue in chronic conditions like obesity, Parkinson disease, hepatitis C infection, cancer, CFS (Neu et al., 2007; Olson et al., 2003; Stone et al., 2000), general population samples (Neu et al., 2010b; Lerdal et al., 2005) and PI (Yang et al., 2009). The FSS is a 9 item 7-point Likert-type scale. Scores are usually reported as 'mean scores' (ranging from 1 to 7) obtained by dividing the total score (ranging from 7 to 63) by 9. For clinically significant pathological daytime fatigue, we used a proposed cut-off >5 on mean scores (Neu et al., 2010b; Lerdal et al., 2005).

The *Epworth Sleepiness Scale* (ESS) is the most widely used scale of subjective sleepiness and daytime sleep propensity. The ESS consists of 8 items (described situations) arranged on a 4-point Likert scale ranging from 0 (''never doze'') to 3 (''high chance of dozing'' during daytime). The summed scores range from 0 to 24 and scores above 10 are commonly interpreted as clinically relevant increased daytime sleepiness (Johns, 1991).

The *Pittsburgh Sleep Quality Index* (PSQI) assesses subjective sleep quality. The 19 items are grouped into seven component scores, each weighted equally on a scale from 0 to 3. These components are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication and daytime dysfunction. The component scores are then summed to yield the global PSQI score. In validation studies, a global PSQI score >5 indicates that a subject is having severe difficulties in at least two areas, or moderate difficulty in more than three areas (Buysse et al., 1989). It has previously been used to quantify NRS in CFS and insomnia (Neu et al., 2007; Moul et al., 2002).

Affective symptoms. The Hospital Anxiety and Depression rating scale (HADRS) is a self-report rating scale of 14 items on a 4-point Likert scale (with a range from 0 to 3). It is designed to measure the intensity of anxiety and depression (7 items for each subscale, HAD-A and HAD-D) symptoms (ranging from 0 to 21). Scores $\geqslant$11 on each subscale have previously been considered as clinically significant (Zigmond and Snaith, 1983). The reliability and validity of the HADRS have been tested in a vast number of studies including CFS (McCue et al., 2006).

2.7. Statistics

Group differences for nominal variables were computed using χ^2 tests. Violations of normality were assessed by means of

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one-sample Kolmogorov–Smirnov tests. Between-group comparisons of normally distributed demographic, psychometric and polysomnographic variables were computed using multivariate analyses of variance (MANOVA). For non-normally distributed variables, Kruskall–Wallis H and Mann–Whitney U tests have been used. For each EEG derivate SWS-relative spectral power was calculated by dividing absolute spectral power in one frequency band by the total power of all frequency bands [e.g. SWS-relative Delta power = $\mu V^2_{Delta\ N3}/(\mu V^2_{US\ N3} + \mu V^2_{Delta\ N3} + \mu V^2_{Theta\ N3} + \mu V^2_{Alpha\ N3} + \mu V^2_{Sigma\ N3} + \mu V^2_{Beta\ N3})$]. Power spectra were standardized using a linear Z-transformation to allow between-group comparisons. Mixed analyses of variance (Mixed ANOVA) were used to test group differences in relative power spectrum distributions. Violations of sphericity were computed by means of Mauchly's tests. Greenhouse-Geisser tests are reported when sphericity is violated. Inspection of higher order polynomials were performed to reveal shape differences in power spectrum distribution within each sleep stage. A posteriori tests were subsequently performed using a sequential Bonferroni (Dunn-Sidak) correction for multiple comparisons. Hypothesis tests were performed two-sided at the 5% significance level. Trends are reported at the 10% level of significance. Statistical analyses were computed using IBM SPSS 20® (Industrial Business Machines, SPSS™ Inc., Chicago, IL).

3. Results

3.1. Demographical and psychometric variables (Table 1)

Descriptive values of biographic and psychometric data are displayed in Table 1. Subject groups present with similar age, BMI, daytime sleepiness (ESS) (Table 1) and gender distribution ($\chi^2(2) = 2.752$, $p = .253$). Perceived sleep quality (PSQI) was worse for PI patients and both patient groups differed significantly from GSC. While CFS patients show numerically highest levels on the FSS, both patient groups display similar but significantly greater fatigue severity compared to GSC (Table 1). Depression symptom intensity (HAD-D) was similar in both patient groups and significantly higher compared to GSC. While displaying a trend for superior anxiety in PI compared to CFS, HAD-A scores are significantly higher in both patient groups compared to GSC (Table 1).

3.2. Polysomnography (Table 1)

With exception of SWS duration and micro-arousal index (MAI), subject groups present with similar measures on all other standard PSG variables (Table 1). Whilst similar between PI and controls, CFS presented with significantly longer SWS duration than controls and PI patients. Both patient groups present with similarly higher sleep fragmentation (as assessed by MAI) than GSC (Table 1).

3.3. Spectral power analysis (Figs. 1 and 2)

Given significant differences in SWS durations between groups (Table 1), spectral power in each defined frequency band was assessed as a relative proportion of the total power within SWS for each EEG electrode derivate.

Fig. 1 shows group differences in standardized SWS relative spectral power distributions for the six computed frequency bands at frontal, central and occipital sites.

Omnibus tests reveal significant differences in standardized relative power spectra distributions between groups during SWS at the frontal ($F(4.364, 139.660) = 4.000$, $p < .005$) and central site ($F(3.338, 106.819) = 3.505$, $p < .05$). Relative power spectra distributions derived from the occipital lead did not show significant differences between subject groups ($F(3.5898, 114.857) = 2.428$, $p = .373$).

Visual inspection of the factorial plots suggests a difference in the curvature of the standardized power spectra distributions among subject groups. At the frontal site, PI patients show larger power proportions in higher frequency bands, whereas GSC and

Table 1
Demographic, psychometric and polysomnographic variables.

	GSC ($n = 22$, 6 males)	CFS ($n = 30$, 4 males)	PI ($n = 15$, 5 males)	MANOVA		Contrast tests (p)		
	M (SD)	M (SD)	M (SD)	F	p	CSC vs. CFS	CSC vs. PI	CFS vs. PI
Age	38.45 (14.2)	44.36 (9.7)	40.87 (10.9)	1.374	.261			
BMI	23.90 (4.8)	24.55 (4.9)	25.7 (4.1)	.643	.529			
TIB	475.68 (46.2)	479.36 (49.7)	472.80 (51.2)	.084	.920			
TST	389.23 (49.8)	387.32 (40.7)	367.67 (47.9)	1.128	.331			
N2	221.14 (42.1)	192.73 (55.6)	206.13 (65.3)	1.536	.224			
SWS	88.27 (37.1)	115.27 (37.5)	88.40 (42.6)	3.347	.042	.024	.992	.043
REM	49.91 (31.8)	47.77 (19.2)	43.93 (21.8)	.251	.779			
HAD-A	5.00 (3.9)	8.14 (4.6)	10.80 (4.1)	8.648	.001	.017	<.001	.065
HAD total	8.00 (5.9)	15.32 (8.3)	19.20 (8.16)	10.963	<.001	.002	<.001	.127
				Kruskall–Wallis		Mann–Whitney U (p)		
	Mdn (Q1; Q3)	Mdn (Q1; Q3)	Mdn (Q1; Q3)	H	p	CSC vs. CFS	CSC vs. PI	CFS vs. PI
SEI	90.90 (87.0; 91.9)	91.40 (85.6; 95.1)	90.46 (76.8; 93.0)	1.006	.605			
SOL	25.75 (16.5; 38.5)	24.50 (14.8; 42.0)	30.00 (12.0; 40.0)	.056	.972			
WASO	40.00 (34.9; 59.0)	35.50 (19.3; 64.5)	38.00 (28.0; 94.0)	1.119	.572			
N1	30.00 (26.6; 41.5)	33.50 (24.8; 44.0)	22.00 (20.0; 34.0)	2.134	.344			
REMlat	86.00 (59.5; 130.5)	94.00 (75.3; 137.5)	94.00 (62.0; 162.0)	2.228	.328			
AHI	2.00 (0.9; 5.0)	3.00 (1.0; 6.0)	2.00 (0.0; 6.0)	1.040	.594			
MAI	15.00 (11.8; 21.9)	29.00 (20.5; 36.8)	29.00 (11.0; 57.0)	12.834	.002	<.001	.035	.923
PLMI	0.00 (0.0; 0.9)	0.00 (0.0:0.0)	0.00 (0.0; 0.9)	2.861	.239			
HAD-D	2.00 (1.0; 4.3)	7.00 (3.8; 9.3)	8.00 (5.0; 9.0)	18.000	<.001	<.001	<.001	.428
ESS	6.50 (2.8; 8.5)	7.50 (3.8; 9.3)	6.50 (4.8; 12.0)	1.046	.593			
FSS	1.77 (1.3; 3.2)	6.00 (5.2; 6.7)	5.22 (4.1; 5.8)	41.083	<.001	<.001	<.001	.401
PSQI	5.00 (2.0; 6.0)	8.50 (6.3; 12.0)	10.5 (7.0; 12.8)	26.079	<.001	<.001	<.001	.015

Good sleeper controls (GSC), chronic fatigue syndrome (CFS), primary insomnia (PI), Body Mass Index (BMI), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale Anxiety Subscale (HAD-A), HAD Depression Subscale (HAD-D), Pittsburgh Sleep Quality Index (PSQI). Time in bed (TIB), Total Sleep Time (TST), Sleep Onset Latency (SOL), Wake After Sleep Onset (WASO), Non Rapid Eye Movement (NREM) Sleep Stage 1 & 2 (N1 & N2), slow wave sleep (SWS), Rapid Eye Movement Sleep (REM) and REM Latency (REMLAT) in minutes (min); Internal Sleep Efficiency Index SEI = (TST/SPT) * 100 in percent and apnea-hypopnea index (AHI) Periodic Limb Movement Index (PLMI) and Micro-Arousal Index (MAI) in events per hour of sleep.

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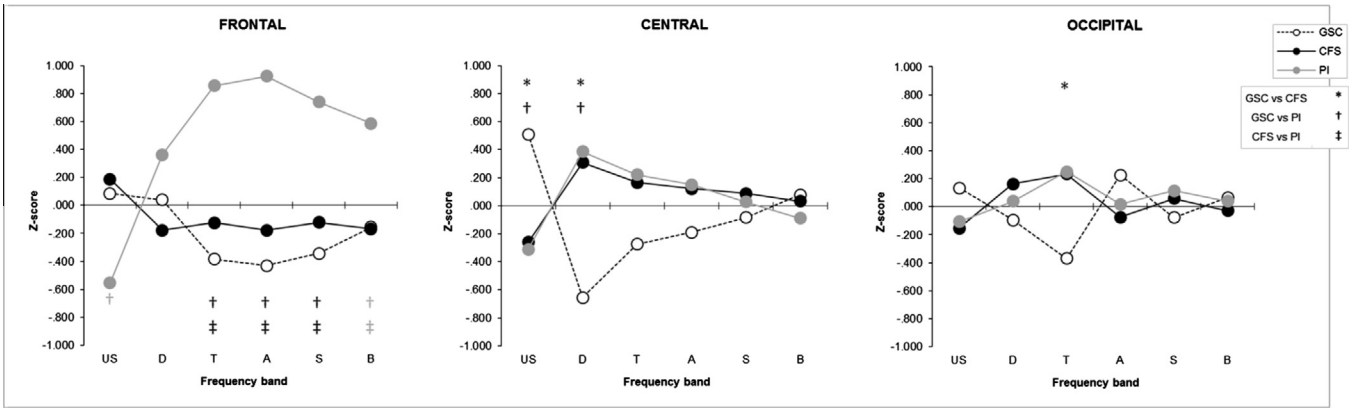

Fig. 1. Standardized SWS-relative spectral power proportions. Ultra slow oscillation (US), delta (D), theta (T), alpha (A), sigma (S), beta (B). Plots show standardized SWS-relative spectral power distributions (as proportions of total SWS spectral power within each frequency band and for each EEG derivate). Provided symbols (*; ‡; †) indicate post-hoc differences between groups at the $p < .05$ (black) or $p < .10$ (grey) levels.

CFS patients show a similar pattern with more evenly distributed power spectra across frequency bands. Statistically, we find that this difference is mainly located in the quadratic term of the interaction between subject groups and relative power spectra distributions ($F(2, 64) = 5.866$, $p < .005$). At the central site, we find similar relative power distributions in CFS and PI patients mainly characterized by lower US and higher delta power in comparison to GSC showing an opposite distribution pattern. Statistically, this difference is supported by a significant interaction between subject groups and relative power proportions mainly located in the 4th order interaction term ($F(2, 64) = 9.721$, $p < .001$).

The abovementioned power spectra proportion differences are confirmed with a posteriori analyses. Compared to GSC, PI patients show significantly higher frontal theta ($d = 1.242$, $p < .001$) alpha ($d = 1.357$, $p < .001$) and sigma power proportions ($d = 1.086$, $p < .005$) and trends towards higher frontal beta power (d=.741, p = .086) and lower frontal US power proportions ($d = -.64$, $p = .060$). Similarly, and when compared to CFS patients, PI patients show significantly higher proportions of frontal theta ($d = .980$, $p < .005$), alpha (d = 1.103, $p < .001$) and sigma power ($d = .862$, $p < .05$) and a trend towards higher proportions of frontal beta power ($d = .755$, $p = .057$). Further, in comparison to GSC, both CFS and PI patients show significantly lower proportions of central US ($d = -.770$, $p < .05$ and $d = -.821$, $p < .05$ respectively) and higher relative central delta power ($d = .966$, $p < .001$ and $d = 1.042$, $p < .005$ respectively). Finally, CFS patients show a trend towards higher occipital theta power proportions compared to GSC ($d = .602$, $p < .095$). All other comparisons returned non-significant.

Additionally, standardized absolute power during SWS showed significantly and similarly lower US power in CFS and PI in comparison with GSC ($d = .748$, $p < .05$ and $d = .803$, $p < .05$ respectively) at the occipital lead only (Fig. 2).

3.4. Explorative pairwise correlations (Fig. 3)

Correlations between spectral power proportions and psychometrics showing significant between-group differences (i.e. PSQI, FSS, HAD) are depicted in Fig. 3. Sleep quality (PSQI) impairment shows a statistically significant correlation to frontal theta and alpha power proportions ($r = .413$, $p < .001$ and $r = .293$, $p < .05$ respectively), to delta and theta power proportions at the central site ($r = .539$, $p < .001$ and $r = .304$, $p < .05$ respectively) and at the occipital site ($r = .279$, $p < .05$ and $r = .338$, $p < .01$ respectively). Further, we find a negative statistically significant correlation between PSQI and central and occipital relative US power (respectively $r = -.457$, $p < .001$ and $r = -.259$, $p < .05$). The severity of fatigue (FSS) is statistically significantly correlated to relative central delta power ($r = .457$, $p < .001$) and relative occipital theta power ($r = .249$, $p < .05$) and shows an inverse correlation to central US power proportions ($r = -.397$, $p < .001$). Intensity of anxiety symptoms (HAD-A) is statistically significantly correlated to proportions of frontal theta, alpha and sigma power ($r = .323$, $p < .05$, $r = .465$, $p < .001$ and $r = .372$, $p < .005$ respectively) and with relative central delta power ($r = .258$, $p < .05$). A fairly similar pattern of associations is found regarding depressive symptoms (HAD-D) showing statistically significant correlations with proportions of frontal theta, alpha and sigma power ($r = .409$, $p < .001$, $r = .491$, $p < .001$ and $r = .337$, $p < .01$ respectively) and with relative central delta power ($r = .353$, $p < .01$). Additionally, we found a statistically significant inverse correlation with depressive symptoms and central US proportions ($r = -.296$, $p < .05$).

4. Discussion

In general, both patient groups showed intense daytime fatigue without EDS and complaints of impaired sleep quality. While fatigue severity was highest in CFS, anxiety symptom intensity was highest in PI and depression symptoms showed similar levels between patient groups. Altered perceived sleep quality, NRS complaints and recurrent un-refreshing morning arousals are commonly associated to affective symptoms in general population samples, PSD and CFS (Neu et al., 2010a,b, 2007). The latter was also the case here, as despite the absence of co-morbid mental disorders, both patient groups presented with higher affective symptom levels than GSC.

With respect to standard PSG variables, patients only differed from GSC for SWS duration and MAI. CFS patients showed longest SWS durations while both patient groups showed similar sleep fragmentation (MAI). This is in line with previous reports of chronic daytime fatigue and increased levels of SWS (Kishi et al., 2011; Neu et al., 2009; Le Bon et al., 2007) or increased levels of NREM stage 4 in CFS (Zubieta et al., 1993) on one hand. And likewise in our sample, where patient groups presented with higher MAI than GSC, proposed previous hypotheses about unspecific NRS or altered sleep quality and sleep often concerned the unspecific presence of increased sleep fragmentation (Neu et al., 2007; Le Bon et al., 2012; Punjabi et al., 1999).

In association to significant sleep quality impairment, daytime fatigue without EDS combined to similar TST, normal or even increased SWS durations in patient groups, spectral power showed here systematically lower central US proportions during SWS in both CFS and PI compared to GSC. In addition, absolute spectral

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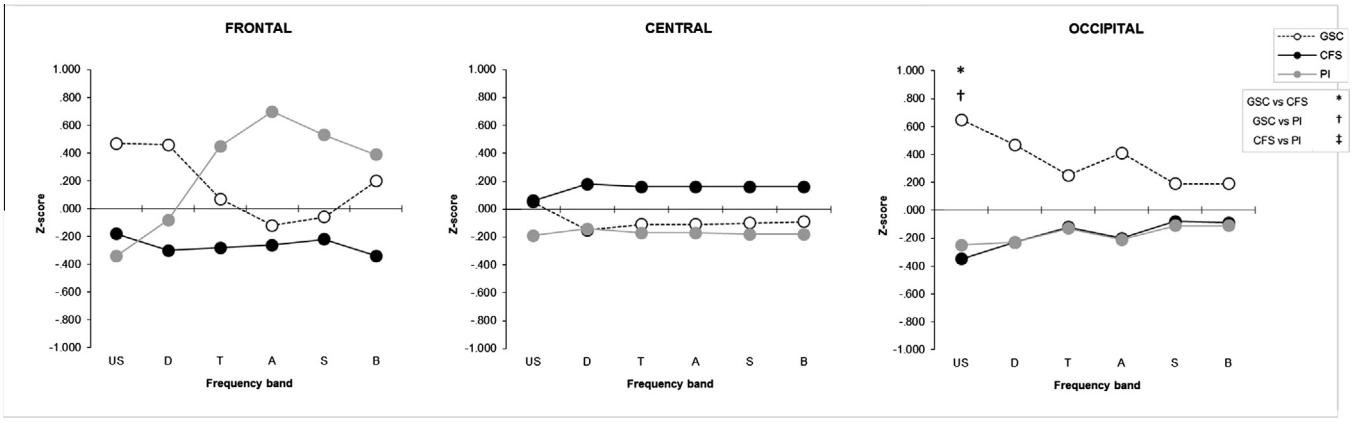

Fig. 2. Standardized absolute spectral power during SWS. Ultra slow oscillation (US), delta (D), theta (T), alpha (A), sigma (S), beta (B). Plots show standardized absolute SWS spectral power distributions of each frequency band and for each EEG derivate. Provided symbols (*; ‡; †) indicate post-hoc differences between groups at the $p < .05$ level.

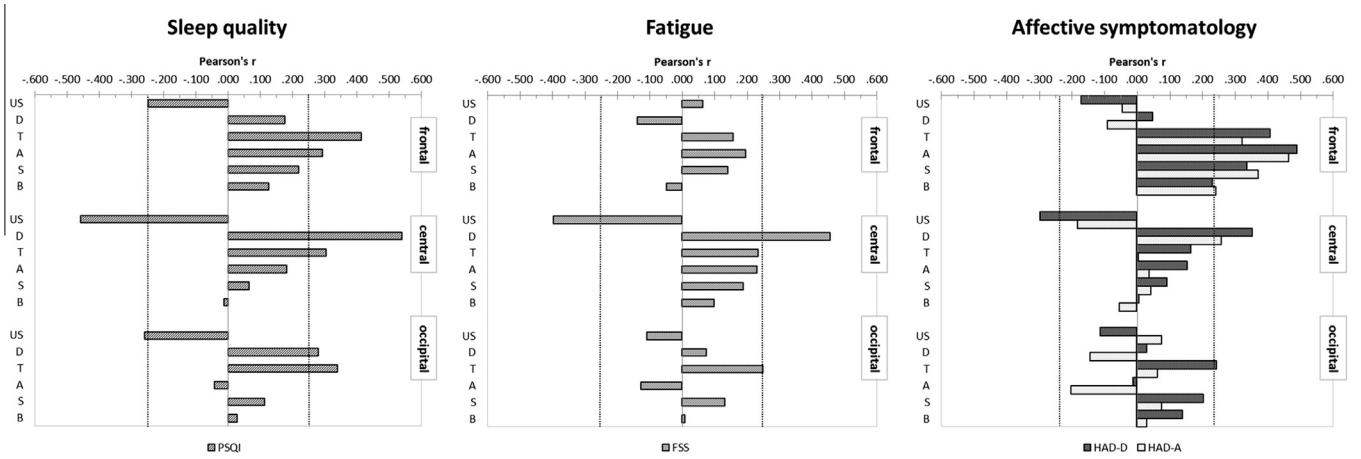

Fig. 3. Correlations between psychometrics and SWS-relative spectral power proportions. Ultra slow oscillation (US), delta (D), theta (T), alpha (A), sigma (S), beta (B). Dotted lines represent significance thresholds at the $p < .05$ level.

power also showed statistically significant lower US power in CFS and PI compared to GSC at the occipital lead. Hence, in association to normal (PI) or increased (CFS) SWS durations, these findings might reflect an impairment in the restorative function of sleep or in sleep homeostasis. Given the related sleep quality impairment, proportions of US activity within SWS, might thus well represent physiological aspects of underlying core restorative functions within sleep. The formerly so-called 'paradoxical' increase of SWS (Le Bon et al., 2007) in chronic fatigue may not be a 'paradox' at all but instead underline the basic difference between sleepiness and fatigue when considering their relationships to sleep. The increased SWS in symptomatic and chronic fatigue conditions might rather reflect an attempt to compensate an intrinsically impaired process (reflected here by decreased US power proportions during SWS). Hence, SWS might even function in an anti-homeostatic manner towards fatigue in CFS for instance. In turn, this explains the sustained systematic NRS complaints and un-refreshing sensations upon morning arousal independently of SPT over 24 h. Unlike in EDS related conditions, sleep per se is not an efficient counter-measure in chronic fatigue conditions.

Based on this hypothesis of potential sleep homeostasis dysfunction in both CFS and PI and taking into account the time spent in SWS, our results show, at the central derivation, a pattern of power spectra distribution, visually suggesting a proportional exchange towards faster frequencies at the expense of US power in CFS and PI patients. The latter is in line with two previous reports on lower US in CFS (compared to controls and to a PSD, i.e. sleep apnea syndrome) (Neu et al., 2014; Le Bon et al., 2012) and consistent with the findings in a study from Krystal et al. (2002) also reporting diminished low-frequency and elevated higher frequency NREM EEG power in subjective insomnia. Likewise in our study these objective findings were also correlated to subjective sleep complaints in patients. Also in line with the present findings, showing PI with higher anxiety levels and increased frontal alpha, beta and sigma power proportions, cortical hyper-arousal and increased wake-drive pressure have previously been related to sleep-related worrying, anxiety symptoms and increased rapid frequency EEG power in insomnia (Feige et al., 2013; Spiegelhalder et al., 2012). Another previous report about increased frontal sigma power associated to increased wake-promoting beta power in insomnia, concluded on possible compensatory effort of such sleep-protecting brain activity, reflected by potentially increased spindle activity, associated to the increase of beta activity in insomnia (Spiegelhalder et al., 2012). Meanwhile, Cervena et al. (2013) have very recently found that increased high beta power was solely present in sleep maintenance insomnia compared to sleep onset insomnia and that alpha power was significantly higher in maintenance insomnia compared to GSCs around sleep onset. In addition, another recent study by Wu et al. (2013) compared PI and GSC waking and NREM EEG power within a frequency range of 0.5–32 Hz. In

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apparent contrast to our results, these authors did not find significant differences in waking or NREM EEG spectral power between groups and concluded that this absence of significant differences might suggest lower degrees of cortical arousal in their PI sample (Israel et al., 2012). Importantly, NREM EEG power of the US band as defined in the present study (0.3–0.79 Hz) had previously not been investigated as such in PI and actual sleep stage relative power proportions accounting for differences in sleep stage duration (like in the present study) had also not been performed in any of these previous studies (Krystal et al., 2002; Spiegelhalder et al., 2012; Wu et al., 2013). The latter might explain discrepancies in comparison with our results.

Included patient groups presented here with clinical conditions defined by two different disorder types. Specific symptoms mainly comprise flu-like symptoms, diffuse muscle or joint pain, sore throat, headaches, post-exertion malaise etc for CFS and sleep initiation, or maintenance difficulties, early morning arousals, sleep-related worrying or anticipative anxiety and a sensation of sleep duration insufficiency for PI respectively. Notwithstanding that PI and CFS are by definition two distinct clinical conditions they also do share unspecific symptoms of NRS and invalidating daytime fatigue without EDS here. Henceforth, shared lower proportions of central US power during SWS may therewith reflect an unspecific sign of sleep related chronic daytime fatigue when combined to NRS. Conversely, our results do also not only confirm specific differences with respect to symptoms (anxiety levels e.g.), but also show significant differences of frontal power distribution between patient groups. To these extents, the exploration of pairwise correlations between psychometric variables and SWS-relative spectral power distributions reveals a rather consistent picture here. The general pattern of proportional exchange with respect to power spectra distributions between higher frequencies at the expense of US power at all sites was associated with impaired perceived sleep quality. Regarding affective symptoms, this pattern seems to be associated with depressive symptoms, primarily for frontal and central sites and we find a similar relationship with reported anxiety symptoms, albeit to a lower extent. For the central lead, the contrast between US and more rapid delta was also significantly related to fatigue severity only. In addition, subjective sleepiness levels (ESS, below clinical thresholds for all groups), did not differ between groups and were not correlated to fatigue (FSS; $r = .115$, $p = .360$). This is also in line with the results from a previous sample of PI patients showing no correlation between sleepiness and fatigue (Valko et al., 2008), further supporting that disregarding unspecific NRS complaints, fatigue in these patients is definitely a different phenomenon than EDS.

Addressing the results from a single night could be considered as a limitation for the present study. Thus, confronting the present results with PSG recordings after habituation might be of interest. However, the stability of power spectra proportions regarding SWA for instance has previously been shown irrespective from standard sleep variables prone to "first night effects". In these terms, it has been stated that "for some measures one night is enough" (Israel et al., 2012). Further, all three groups were studied under similar conditions and results of standard sleep parameters showed anyhow only minimal differences between groups. In addition, despite NREM sleep and SWS in particular representing brain states of high synchronization, the latter does not necessarily mean power equality between hemispheres. With respect to the chosen PSG recording method here, the present findings should therefore also be carefully considered as solely limited to the right hemisphere. Bihemispheric or preferably high density sleep-EEG should provide further insight about this matter.

In summary, we found consistent evidence for lower power proportions of slow oscillations in SWS in clinical conditions defined by chronic daytime fatigue which is not EDS or increased sleep propensity. In combination with normal (PI) or even increased SWS durations or proportions (CFS), these findings point towards compensation of a qualitatively altered process within SWS, potentially expressing homeostatic dysregulation. Though, our results imply that lower proportions of US power may indeed be an unspecific sign of sleep related chronic daytime fatigue combined to NRS but do also confirm specific differences between both patient groups with respect to psychometrics on one hand and relative frontal power distribution during SWS on the other. Previous findings and the present results suggest that the evaluation of SWS durations may be considered in chronic fatigue conditions like CFS. The latter might become clinically useful in the future, in particular if confirmatory studies reflect similar findings and if the precision of SWS durations or proportions' thresholds for given age ranges improves over the next years. Further, we suggest that the assessment of slow oscillation power (<1 Hz) should be considered when conducting research in fatigue related conditions like insomnia and CFS. In chronic fatigue conditions associated to NRS complaints, sleep might indeed, in contrast to EDS related conditions, not present as a relative quantitative loss of SWS or SWA (resulting in higher homeostatic pressure and increased sleep propensity) as in these challenged situations (sleep deprivation e.g.) but rather as a qualitative change or modification of relative spectral power distributions within SWS or slow wave activity itself (i.e. presenting here as relative US power decrease and an implicit power shift towards higher frequency bands).

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Disclosure

On behalf of all co-authors, I hereby declare that none of us had any conflicts of interests concerning the present study.

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